1: Neurosurgery 1997 Jan;40(1):141-51

Inhibition of epidermal growth factor receptor-associated tyrosine kinase blocks glioblastoma invasion of the brain.

Penar PL, Khoshyomn S, Bhushan A, Tritton TR.

Division of Neurosurgery, University of Vermont College of Medicine, Burlington, USA.

OBJECTIVE: Glioblastoma multiforme is a malignant primary brain tumor associated with short patient survival despite aggressive treatment, in part because of its propensity to aggressively infiltrate into brain tissue. Glioblastoma multiforme is also unique because it is the only nonepithelial human tumor for which excessive activation of epidermal growth factor receptor (EGFR) has been consistently linked to tumor growth and patient survival, and EGFR activation promotes glioblastoma multiforme infiltration in vitro. METHODS: Cocultures of human glioblastoma spheroids (derived from three separate patients) and fetal rat brain aggregates were examined for infiltration using confocal microscopy, in the presence of 0 to 100 mumol/L genistein, a tyrosine kinase (TK) inhibitor, and 3 mumol/L tyrphostin A25, a specific EGFR-TK inhibitor. RESULTS: Infiltration (not attachment) was completely inhibited by genistein at 10 mumol/L, the IC20 for monolayer growth inhibition in two cell lines. Tyrphostin A25 at 3 mumol/L (the IC20 for monolayers) reduced invasion in a third cell line from 38.8 +/- 6.1% invasion-hour per hour (n = 5) to 2.9 +/- 1.2% invasion-hour per hour (n = 6) (P = 0.0002, two-tailed t test, 93% inhibition), and from 0.54 +/- 0.065% per hour (slope) to 0.028 +/- 0.018% per hour (P = 0.00001, 95% inhibition). Maximal percent invasion was reduced from 100 +/- 0 to 7.4 +/- 5.6% of the fetal rat brain aggregate. No change was detected in EGFR-associated tyrosine phosphorylation at those doses in monolayers by 32P immunolabeling, consistent with the known effects of low concentrations of TK inhibitors. An increase in expression of wild-type and truncated EGFR was demonstrated by Western blotting. Invasion was equally well inhibited by a monoclonal antibody to the high-affinity ligand binding domain of EGFR and not by antibody to an inactive domain. CONCLUSION: Our observations support the role of EGFR activation as a determinant by which glioblastoma invades normal brain tissue, and we show that invasion can be effectively inhibited at much lower concentrations of TK inhibitors than are necessary for growth suppression.

PMID: 8971836 [PubMed - indexed for MEDLINE]

1: Gastroenterology 1998 May;114(5):930-9

Inhibition of epidermal growth factor receptor kinase induces protease-dependent apoptosis in human colon cancer cells.

Karnes WE Jr, Weller SG, Adjei PN, Kottke TJ, Glenn KS, Gores GJ, Kaufmann SH.

Division of Gastroenterology, Mayo Clinic, Rochester, Minnesota 55905, USA.
karnes@ralph.mayo.edu

BACKGROUND & AIMS: The epidermal growth factor receptor (EGFR) is under investigation as a therapeutic target for cancers. Colon cancer cell lines are variably dependent on autocrine stimulation of EGFR. We therefore examined the effects of a selective EGFR tyrosine kinase inhibitor, PD 153035, on proliferation and survival of five colon cancer cell lines whose autonomous proliferation is either EGFR ligand dependent or EGFR ligand independent. METHODS: Effects of inhibitors were screened by MTS growth assays, [3H]thymidine incorporation, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling assay, fluorescence microscopy, immunoblotting, and in vitro protease assays. RESULTS: PD 153035 caused dose-dependent cytostasis (200 nmol/L to 1 micromol/L) and apoptosis (>10 micromol/L) in ligand-dependent cell lines and caused variable apoptosis (>10 micromol/L) but no cytostasis in ligand-independent cell lines. Apoptosis induced by 10 micromol/L PD 153035 was not associated with induction of p53 protein expression but was accompanied by activation of caspases that cleave poly(ADP-ribose) polymerase, lamin B1, and Bcl-2. Inhibition of caspase 3-like protease activity by DEVD-fluoromethylketone significantly delayed the onset of PD 153035-induced apoptosis. CONCLUSIONS: The EGFR tyrosine kinase inhibitor PD 153035 induces cytostasis and caspase-dependent apoptosis in EGFR ligand-dependent colon cancer cell lines. These observations encourage further investigation of EGFR tyrosine kinase inhibitors for treatment of colorectal neoplasms.

PMID: 9558281 [PubMed - indexed for MEDLINE]

[LinkDB | SSDB | FASTA-genes | FASTA-sp | BLAST-nr | SOSUI | PSORT | MOTIF]

ENTRY 24329 CDS R.norvegicus
NAME Egfr
DEFINITION epidermal growth factor receptor
POSITION 14q22
DBLINKS LocusLink: 24329
RGD: 2543
RATMAP: 33902
NCBI: 25742617

CODON_USAGE

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AASEQ 1209

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